30 May 2024
EMA/341648/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Pomalidomide Krka

International non-proprietary name: Pomalidomide

Procedure No. EMEA/H/C/006314/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADR	Adverse drug reactions
AE	Adverse events
ANOVA	Analysis of variance
API	Active pharmaceutical ingredient
AR	Assessment report
ASMF	Active substance master file = drug master file
BDL	Below the limit of detection
BEQ	Bioequivalence
CEP	Certificate of suitability of the EP
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
Cmax	maximum (or peak) serum concentration
CoA	Certificate of analysis
EC	European Commission
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Environmental risk assessment
EU	European Union
FP	Finished product
FPM	Finished product manufacturer
GC	Gas chromatography
GCP	Good clinical practice
GLP	Good laboratory practice
GMP	Good manufacturing practice
HCL	Hydrochloric acid
HDPE	High density polyethylene
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICP-MS	Inductively coupled plasma mass spectrometry
IPC	In-process control test
IR	Infrared
KF	Karl Fischer titration
LDPE	Low density polyethylene
LLOQ	Lower limit of quantification
LoA	Letter of access
LoD	Limit of detection
LOD	Loss on drying
LoQ	Limit of quantitation
LoQ	List of questions

MAH	Marketing authorisation holder
MO	Major objection
MS	Mass spectroscopy
NLT	Not less than
NMR	Nuclear magnetic resonance
NMT	Not more than
OPA/Al/PVC	Oriented polyamide/aluminium/polyvinyl chloride
/PET/Al	/polyethylene terephthalate/ aluminium
PDE	Permitted daily exposure
Ph. Eur.	European Pharmacopoeia
PIL	Patient information leaflet
RH	Relative humidity
rpm	revolutions per minute
RRMM	Relapsed /refractory multiple myeloma
RSD	Relative standard deviation
SmPC	Summary of product characteristics
TLC	Thin layer chromatography
TSE	Transmissible spongiform encephalopathy
Tmax	Time at which the Cmax is observed
TEAEs	Treatment emergent adverse events
UV	Ultra-violet
XR(P)D	X-ray (powder) diffraction

Not all abbreviations may be used.

1. Background information on the procedure

1.1. Submission of the dossier

The applicant KRKA, d.d., Novo mesto submitted on 9 August 2023 an application for marketing authorisation to the European Medicines Agency (EMA) for Pomalidomide Krka, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 30 March 2023.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indications:

> Pomalidomide Krka in combination with bortezomib and dexamethasone is indicated in the treatment of adult patients with multiple myeloma who have received at least one prior treatment regimen including lenalidomide.
>
> Pomalidomide Krka in combination with dexamethasone is indicated in the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data and a bioequivalence study with the reference medicinal product Imnovid instead of non-clinical and clinical unless justified otherwise.

The chosen reference product is:

- Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 10 years in the EEA: Product name, strength, pharmaceutical form: Imnovid, 1mg, 2mg, 3mg, 4mg, capsules hard
- Marketing authorisation holder: Bristol-Myers Squibb Pharma EEIG
- Date of authorisation: 05-08-2013
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number:
- 1mg - EU/1/13/850/001; 005
- 2mg - EU/1/13/850/002; 006
- 3mg - EU/1/13/850/003; 007

- 4mg - EU/1/13/850/004; 008

Medicinal product authorised in the Union /Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Imnovid, 1mg, 2mg, 3mg, 4mg, capsules hard
- Marketing authorisation holder: Bristol-Myers Squibb Pharma EEIG
- Date of authorisation: 05-08-2013
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number:
- 1mg - EU/1/13/850/001; 005
- 2mg - EU/1/13/850/002; 006
- 3mg - EU/1/13/850/003; 007
- 4mg - EU/1/13/850/004; 008

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Imnovid, 4mg, capsules hard
- Marketing authorisation holder: Bristol-Myers Squibb Pharma EEIG
- Date of authorisation: 05-08-2013
- Marketing authorisation granted by:
  - Union
- Marketing authorisation number(s): EU/1/13/850/004; 008
- Bioavailability study number(s): Study code: 22-741

1.3. Information relating to orphan market exclusivity

1.3.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.4. Scientific advice

The applicant did not seek scientific advice from the CHMP.

1.5. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Ewa Balkowiec Iskra

The application was received by the EMA on	9 August 2023
The procedure started on	28 September 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	11 December 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	3 January 2024
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	25 January 2024
The applicant submitted the responses to the CHMP consolidated List of Questions on	22 February 2024
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on	02 April 2024
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	11 April 2024
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	25 April 2024
The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on	30 April 2024
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	14 May 2024
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Pomalidomide Krka on	30 May 2024
The CHMP adopted a report on similarity of Pomalidomide Krka with Kyprolis (carfilzomib), Imnovid (pomalidomide), Ninlaro (ixazomib), Farydak (panobinostat), Darzalex (daratumumab), Blenrep (belantamab mafodotin), Abecma (idecabtagene vicleucel), Carvykti (Ciltacabtagene autoleucel) and Talvey(talquetamab)	30 May 2024

2. Scientific discussion

2.1. Introduction

This application concerns a generic application of a centrally authorised medicinal product according to Article 10(1) of Directive 2001/83/EC as amended.

The applicant has developed Pomalidomide Krka capsule, hard as generic to the reference product Imnovid 1 mg, 2 mg, 3 mg, 4 mg hard capsule.

The indication, posology and pharmacology as presented in the proposed SmPC are shown below.

Therapeutic indication

Pomalidomide Krka in combination with bortezomib and dexamethasone is indicated in the treatment of adult patients with multiple myeloma who have received at least one prior treatment regimen including lenalidomide.

Pomalidomide Krka in combination with dexamethasone is indicated in the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy.

Posology and method of administration

The posology and method of administration are in line with the reference product.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as hard capsules containing 1 mg, 2 mg, 3 mg or 4 mg of pomalidomide.

Other ingredients are: capsule contents for all strengths – Isomalt, crospovidone (type A), hydroxypropylcellulose, low-substituted, sodium stearyl fumarate

Capsule shell 1 mg strength – Gelatin, titanium dioxide (E171), Iron oxide yellow (E172), Indigo carmine (E132) and the printing ink: shellac, iron oxide black (E172), potassium hydroxide.

Capsule shell 2 mg strength – Gelatin, titanium dioxide (E171), iron oxide yellow (E172), iron oxide red (E172), indigo carmine (E132) and the printing ink: shellac, titanium dioxide (E171), potassium hydroxide.

Capsule shell 3 mg strength – Gelatin, titanium dioxide (E171), iron oxide yellow (E172), indigo carmine (E132) and the printing ink: shellac, titanium dioxide (E171), potassium hydroxide.

Capsule shell 4 mg strength – Gelatin, titanium dioxide (E171), indigo carmine (E132) and the printing ink: shellac, titanium dioxide (E171), potassium hydroxide.

The product is available in perforated unit dose blisters (OPA/Al/PVC//PET/Al) as described in section 6.5 of the SmPC.

2.2.2. Active substance

2.2.2.1. General Information

The chemical name of pomalidomide is 4-amino-2-(2,6-dioxo-3-piperidyl)isoindoline-1,3-dione corresponding to the molecular formula $C_{13}H_{11}N_3O_4$. It has a relative molecular mass of 273.25 g/mol and the following structure:

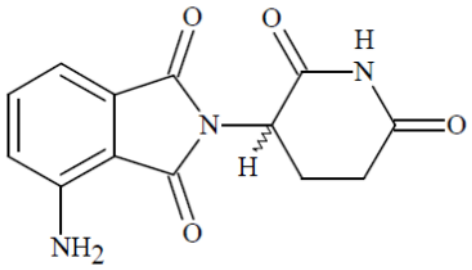


Figure 1: active substance structure

The chemical structure of pomalidomide was elucidated by a combination of IR, UV, ^{1}H-NMR, ^{13}C-NMR, MS, and elemental analysis. The solid-state properties of the active substance were measured by XRPD.

Pomalidomide is a light yellow to yellow coloured powder, soluble in dimethylsulfoxide and in dimethylformamide, but insoluble in aqueous media across the physiological pH range. It is non-hygroscopic and is micronised to produce a defined particle size range.

Pomalidomide exhibits stereoisomerism due to the presence of one chiral centre. The active substance is manufactured as a racemic mixture of the *R*(+) and *S*(-) enantiomers. This stereocentre originates in the starting material as a single enantiomer and is epimerised during the process. Specific optical rotation data has been presented for 10 batches of the active substance showing that a racaemic mixture of the active substance is produced. Therefore, it is not considered necessary to include a test for stereochemistry in the final specification of the active substance.

Polymorphism has been observed for pomalidomide. Three polymorphic forms are reported, form-A, form-B, and an amorphous form. The active substance manufacturing process has been shown to consistently produce a stable polymorphic form. The polymorphic form is controlled in the specification of the active substance.

2.2.2.2. Manufacture, characterisation and process controls

The active substance is manufactured by one manufacturing site supported by an ASMF. Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

Pomalidomide is synthesised in six main steps using well defined starting materials with acceptable specifications.

One of the initially proposed starting materials was not acceptable, and a major objection (MO) was raised on this aspect. The applicant and ASMF holder were requested to redefine one of the starting materials to earlier in the synthetic process in order for an important reaction to be carried out within the synthetic process of the active substance. The applicant & ASMF holder suitably redefined the starting material as requested and provided the relevant required information concerning this starting material. The MO was therefore considered resolved.

Adequate in-process controls are applied during the synthesis and specifications and control methods for intermediate products, starting materials, and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

The active substance is packaged in an LDPE bag, which is placed into a black LDPE bag and placed in a HDPE drum, the material complies with Commission Regulation (EU) 10/2011, as amended.

2.2.2.3. Specification(s)

The active substance specification includes tests for: description (visual), identification (IR, HPLC), polymorphic form (XRPD), solubility (Ph. Eur.), loss on drying (Ph. Eur.), water content (KF), sulphated ash (Ph. Eur.), related substances (HPLC), assay (HPLC), residual solvents (GC), particle size (laser light diffraction) and elemental impurities (ICP-MS).

No impurities are present at higher than the qualification threshold according to ICH Q3A.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay testing has been presented.

Batch analysis data for 5 batches, including 3 at commercial scale, of the active substance are provided. The results are within the specifications and consistent from batch to batch.

2.2.2.4. Stability

Stability data from 3 pilot scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 60 months under long term conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. In addition to this, 12 months of long-term stability data, and 6 months of accelerated stability data were provided for 3 commercial scale batches under the same conditions.

The following parameters were tested*:* description, identification, solid state form, loss on drying, water content, related substances, assay. The analytical methods used were the same as for release and were stability indicating.

Under long term and accelerated conditions, all tested parameters were within the specifications and no trends are observed.

With respect to ongoing stability studies, any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

Photostability testing following the ICH guideline Q1B was performed on 1 batch. Results under stressed conditions (acidic, basic, oxidative, temperature) were also provided on 1 batch. Under acidic, basic, and strong oxidative conditions significant degradation was observed with decreases in assay values and increases in impurity results. The active substance is not sensitive to light.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 60 months with the applicant’s selected storage condition.

2.2.3. Finished medicinal product

2.2.3.1. Description of the product and pharmaceutical development

The finished product is formulated as hard capsules containing the active substance pomalidomide. Each hard capsule contains 1 mg, 2mg, 3 mg or 4 mg of the active substance. The visual appearance of each strength is as follows:

1 mg: Hard, gelatine capsules, size 2. Capsule length: 17.3±0.5 mm. Body of the capsule is light yellow to brownish yellow with black mark 1. Capsule cap is blue. Content of the capsule is light yellow to yellow powder.

2 mg: Hard, gelatine capsules, size 2. Capsule length: 17.3±0.5 mm. Body of the capsule is orange to brownish orange with white mark 2. Capsule cap is blue. Content of the capsule is light yellow to yellow powder.

3 mg: Hard, gelatine capsules, size 2. Capsule length: 17.3±0.5 mm. Body of the capsule is bluish green with white mark 3. Capsule cap is blue. Content of the capsule is light yellow to yellow powder.

4mg: Hard, gelatine capsules, size 2. Capsule length: 17.3±0.5 mm. Body of the capsule is light blue with white mark 4. Capsule cap is blue. Content of the capsule is light yellow to yellow powder.

The aim of development was to create a generic product equivalent to the reference product Imnovid. The proposed product contains different excipients to the reference product, and the excipient of known effect isomalt is present in the proposed product. This excipient, which is not present in the reference product, is reflected in the product information of the proposed product with relevant warnings.

The active substance is poorly soluble and the physical characteristics which could impact the *in-vivo* performance of the finished product are suitably controlled in the specification of the active substance. A control is included for particle size distribution and the relevant polymorphic form of the active substance.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The 4 mg strength of the proposed product was compared to the reference product in a bioequivalence study, and the results of this study were acceptable. Please refer to the clinical section of this report for further detail of the bioequivalence study performed. The dissolution profiles of the 4 mg strengths of the proposed and reference product used in the bioequivalence studies were found to be not similar. The *in vivo* results of the bioequivalence study take precedence over these *in vitro* dissolution comparisons.

A biowaiver was applied for the lower strengths of the proposed product, this was based on the acceptable bioequivalence study conducted with the 4 mg strength and the fact that all relevant criteria specified in the guideline in the investigation of bioequivalence were met for the lower strengths. These strengths are manufactured by the same process, have the same qualitative composition, the amount of active substance is <5% of the capsule content weight and only the filler is changed to accommodate any differences. *In vitro* dissolution results at three pH testing conditions (pH 1.2, 4.5 and 6.8) demonstrated that the dissolution profiles for each of the strengths were similar to the profile of the 4 mg proposed product used in the bioequivalence study.

The manufacturing process was developed to use a simple blending and capsulation method based on standard equipment and commercially available capsule sizes. The blending step was identified as a critical process to ensure content uniformity, and the suitability of the critical process parameters for this step were confirmed during the process validation studies. It was also confirmed that the finished product manufacturing process does not impact the polymorphic form of the active substance.

The dissolution method has been appropriately developed and the discriminatory power of the QC dissolution method has been demonstrated. The method is discriminatory with respect to particle size of the active substance.

The primary packaging is peel open, child resistant, perforated unit dose blisters (OPA/Al/PVC//PET/Al). The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.2.3.2. Manufacture of the product and process controls

The manufacturing process consists of three main steps: blending, capsulation & packaging. The process is considered to be a non-standard manufacturing process due to the low content of the active substance. The process is to be conducted at one manufacturing site.

Major steps of the manufacturing process have been validated by process validation studies on three commercial scale batches of each strength. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

2.2.3.3. Product specification(s)

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form, appearance (visual), content uniformity (Ph. Eur.), identification (TLC, HPLC), related substances (HPLC), assay (HPLC), water (KF), dissolution (HPLC), and microbiological quality (Ph. Eur.).

The limits for related substances have been set in line with ICH Q3B requirements, and no impurities at levels exceeding the relevant qualification threshold have been detected.

The initially proposed limit for dissolution had not been set in line with the biobatch performance and the requirements of the reflection paper on the dissolution specification for generic solid oral immediate release products with systemic action (EMA/CHMP/CVMP/QWP/336031/2017). As this aspect could impact the *in-vivo* performance of the product, an MO was raised on this aspect, and maintained during the procedure. The MO was suitably resolved when the applicant revised the limit as required in line with the relevant reflection paper.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on three batches using a validated ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and

answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used has been presented.

Batch analysis results are provided for three production scale batches of each strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

2.2.3.4. Stability of the product

Stability data from three commercial scale batches of finished product stored for up to eighteen months under long term conditions (25ºC / 60% RH) and for up to six months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are representative of those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, water content, assay, related substances, dissolution and microbiological quality. The analytical methods used were the same as for release and are stability indicating. No out of specification results or out trends were observed under long term or accelerated stability testing conditions, and no significant trends were observed, the product is stable under these conditions.

The finished product is susceptible to moisture absorption leading to increases in water content, for this reason an instruction to store in the packaging to protect from moisture is proposed.

With respect to ongoing stability studies, in accordance with EU GMP guidelines, any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

In addition, one commercial scale batch of each strength was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products, and the product was shown to be photostable.

Based on available stability data, the proposed shelf-life of 24 months and "store in the original package in order to protect from moisture" as stated in the SmPC is acceptable.

2.2.3.5. Adventitious agents

Gelatine obtained from bovine sources is used in the product. Valid TSE CEP from the suppliers of the gelatine used in the manufacture is provided.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that

the product should have a satisfactory and uniform performance in clinical use.

During the procedure two MOs on quality aspects were raised, these concerned the selection of one of the initially proposed starting materials for the active substance, and the initially proposed dissolution limit for the finished product. The MO concerning the starting material was suitably resolved by redefining the starting material to an earlier step in the synthetic process and the provision of the required information on the newly proposed starting material. The MO on the dissolution limit for the finished product was resolved when the applicant revised the dissolution limit to be in line with the performance of the biobatch.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Relevant information has been presented to give reassurance on TSE safety.

2.2.6. Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment studies were submitted. This was justified by the applicant as the introduction of Pomalidomide Krka manufactured by KRKA, d.d., Novo mesto is considered unlikely to result in any significant increase in the combined sales volumes for all Pomalidomide containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar.

2.3.3. Discussion on non-clinical aspects

The applicant has not performed non-clinical studies. Non-clinical data are submitted from published literature data. This is reasonable and acceptable since pomalidomide is a well-known active substance. Grounds for not providing new non-clinical data are adequately justified.

The SmPC sections 4.6 and 5.3 are in line with those for the innovator Imnovid, 1 mg, 2 mg, 3 mg, 4 mg capsule, hard, registered by Bristol-Myers Squibb Pharma EEIG and are therefore acceptable.

The ERA submitted by the applicant is acceptable.

2.3.4. Conclusion on the non-clinical aspects

Data presented are acceptable from the non-clinical point of view. There are no objections to the approval of Pomalidomide Krka 1 mg, 2 mg, 3 mg, 4 mg capsule, hard from a non-clinical point of view.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for hard capsules containing pomalidomide. To support the marketing authorisation application the applicant conducted one bioequivalence study with a cross-over design under fasting conditions. This study was the pivotal study for this application.

No formal scientific advice by the CHMP was given for this medicinal product. For the clinical assessment Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1) in its current version is of particular relevance.

GCP aspect

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Exemption

A strength biowaiver was requested for Pomalidomide Krka 1 mg, 2 mg and 3 mg hard capsules.

In support of this biowaiver the applicant performed *in vitro* dissolution studies at three different buffers (0.1M hydrochloric acid, acetate buffer solution pH 4.5 and phosphate buffer solution pH 6.8), with the test product that was used in the pivotal bioequivalence study (BEQ batch 4mg) and additional strengths of 1mg, 2mg and 3 mg of the test product. Dissolution tests were conducted under standard dissolution conditions with paddle apparatus (rotation speed of 50 rpm).

Manufacturing process and manufacturing site for the production of pomalidomide capsules, hard is the same for all strengths.

The amount of pomalidomide in all developed strengths represents less than 5% of capsule content weight. In all strengths the amount of all excipients constant, except for the filler, which was changed to compensate for the difference in the amount of pomalidomide to obtain the same total weight in all developed strengths. This is in line with the EMA Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **), section 4.1.6 considering general biowaiver criteria.

In all three dissolution comparisons, except for pomalidomide 3 mg strength in pH 6.8 more than 85% of pomalidomide is dissolved within 15 minutes. For Pomalidomide 3 mg strength in pH 6.8, 85% of pomalidomide was dissolved within 15 minutes. However, the f2 similarity factor calculated for 3 mg strength was 89. In line with Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr ** an f2 value between 50 and 100 suggests that the two dissolution profiles are similar.

In conclusion, based on the provided results of *in vitro* dissolution study, a waiver for a bioequivalence study can be agreed for strengths of 1mg, 2mg and 3 mg since the *in vitro* dissolution profiles of pomalidomide 1mg, 2mg and 3 mg performed in three different buffers (pH 1.2, 4.5 and 6.8) were similar to that of the 4 mg strength.

Tabular overview of clinical studies

To support the application, the applicant has submitted one bioequivalence study and one comparative bioavailability study.

Table 1. Tabular overview of clinical studies

Type of Study	Study Identifier	Location of Study Report	Objective of the Study	Study Design; Type of Control	Test Product(s); Dosage Regimen; Rout of Administration	No. of Subjects	Healthy Subjects/ Diagnosis of Patients	Duration of Treatment	Study Status; Type of report
BE	22-741	Section 5.3.1.2.	Demonstration of bioequivalence of test to reference capsule formulations under fasting conditions	Open-label, single-dose, randomized, two-period, two treatment, two-sequence, crossover, bioequivalence study 7 days wash-out period fasting conditions	**Test Product:** Pomalidomide 4 mg capsules, hard (B. No.: RA0440) One capsule of the test formulation in one period / 4 mg of pomalidomide per capsule / Oral **Reference Products:** Imnovid® 4 mg hard capsules (B. No.: C2437AH) One capsule of the reference formulation in one period / 4 mg of pomalidomide per capsule / Oral	28	Healthy male subjects	Single Dose	Complete; Full
BA	22-725	2.7.6	Comparative bioavailability study	Open-label, single-dose, randomized, four-period, four treatment, four -sequence, crossover, bioavailability study	**Test 1 Product:** Pomalidomide 4 mg capsules, hard (B. No.: Y00742) **Test 2 Product:** Pomalidomide 4 mg capsules, hard (B. No.: Y00743) **Test 3 Product:** Pomalidomide 4 mg capsules, hard (B. No.: Y00744) One capsule of the test formulation in one period / 4 mg of pomalidomide per capsule / Oral **Reference Products:** Imnovid® 4 mg hard capsules (B. No.: C2329A) One capsule of the reference formulation in one period / 4 mg of pomalidomide per capsule / Oral	18	Healthy male subjects	Single Dose	Complete, Abbreviated

2.4.2. Clinical pharmacology

2.4.2.1. Pharmacokinetics

Study 22-741: A Single-Dose, Bioequivalence Study of Two Formulations of Pomalidomide 4 mg Capsules, Hard under Fasting Conditions.

Study Initiation: November 29, 2022
Study Completion: December 17, 2022

Methods

- **Study design**

This was an open-label, single-dose, randomised, two-period, two-treatment, two-sequence, crossover, bioequivalence study, designed to evaluate the bioequivalence of pomalidomide between a test and a reference formulation in healthy, non-smoking, male subjects from 18 to 55 years under fasting conditions.

In each period, subjects were administered a single, oral dose of the Test Product (Treatment A) or Reference Product (Treatment B), in accordance with the randomisation scheme, after an overnight fast of at least 10 hours.

A single, oral dose of either the Test Product or Reference Product in each of the two periods, separated by a 7- day washout between drug administrations.

The 4 mg strength of pomalidomide was used for this bioequivalence study in compliance with the applicable guidance document.

Subjects were randomly assigned to one of the two treatment sequences, according to a predetermined, computer-generated randomisation scheme.

Concentrations of pomalidomide were measured from plasma PK samples using a validated LCMS/ MS analytical method over a 48-hour interval after investigational medicinal product (IMP) administration.

The primary objective of this study was to evaluate the bioequivalence of pomalidomide from the Test Product, (Treatment A) versus the Reference Product (Treatment B) after a single dose in healthy male subjects under fasting conditions.

The secondary objective of this study was to evaluate the safety and tolerability of the study treatments.

- **Test and reference products**

Test Product (Treatment A):
Pomalidomide 4 mg capsules, hard
Batch No.: RA0440
Batch Size: 30.000 capsules
(Manufacturer: KRKA-FARMA d.o.o., Republic of Croatia, EU)
Dose: 4 mg
Mode of Administration: Oral under fasting conditions

Reference Product (Treatment B):
Imnovid 4 mg hard capsules (pomalidomide)
Batch No.: C2437AH
(MAH: Celgene Europe B.V., The Netherlands, EU;
Manufacturer: Celgene Distribution B.V., The Netherlands, EU)
Dose: 4 mg
Mode of Administration: Oral under fasting conditions

Both the reference and the test products are identical with regards to the strength and formulation intended to be marketed. CoA of the test and reference batches have been provided in the Study Protocol. Test Product Batch size was 30.000 capsules.

Population studied

Main Criteria for Inclusion:

The study population included non-smoking, male subjects, 18 to 55 years of age, with a body mass index ≥18.5 to ≤30 kg/m^2, who were deemed healthy based upon a medical history, 12-lead electrocardiogram (ECG), laboratory evaluation (haematology, biochemistry, serology, and urinalysis), physical examination, vital signs measurements (blood pressure, pulse rate, respiration rate, and temperature). Eligible subjects had negative test results for urine cotinine and urine drugs of abuse at screening. Inclusion and exclusion criteria are acceptable.

Number of Subjects:

• Planned for inclusion, randomised and enrolled into the study: 28 subjects.

• Completed the study: 27 subjects.

One subject discontinued from the study immediately after Period 1 drug administration for personal reasons.

• Included in the safety analysis: 28 subjects.

• Included in the PK and statistical analyses: 27 subjects.

The subject who discontinued from the study did not accrue sufficient data to allow for the estimation of Cmax and/or AUC parameters in both periods. As such, the subject's data were excluded from the PK and statistical analyses.

Protocol deviations

No major protocol deviations were reported.

- **Analytical methods**

The aim of the analysis submitted in report PMRI-1855-20 was to validate a liquid chromatographic tandem mass spectrometric method for determination of pomalidomide in human plasma to support pivotal clinical study - 22-741.

The achiral analytical method was employed for this study. The applicant justified the use of the achiral method.

The analysis of pomalidomide was successfully validated in the linear ranges of the analyte from 0.500 ng/mL to 150.000 ng/mL. QC sample for pomalidomide were 0.500 ng/mL, 1.500 ng/mL, 60.000 ng/mL, 90.000 ng/mL.

Intra-day and inter-day precision and accuracy were acceptable and were as follow: Intra-day precision (%) for the lower limit of quantification (LLOQ) 6.5 - 12.1; QC A 1.50 ng/mL 3.1 - 4.2; QC B 60.0 ng/mL 1.9 - 2.4; QC C 90.0 ng/mL 1.1 - 6.0. Intra-day accuracy (%) for LLOQ 0.500 ng/mL 81.6 - 100.2; QC A 1.50 ng/mL 97.3 - 100.7; QC B 60.0 ng/mL 98.3 - 102.5; QC C 90.0 ng/mL 98.2 - 107.3. Inter-day precision (%) LLOQ QC 0.500 ng/mL 12.3; QC A 1.50 ng/mL 3.9; QC B 60.0 ng/mL

2.8; QC C 90.0 ng/mL 5.7. Inter-day accuracy (%) for LLOQ QC 0.500 ng/mL 93.2; QC A 1.50 ng/mL 100.0; QC B 60.0 ng/mL 100.8 and QC C 90.0 ng/mL 101.3.

The following parameters were also addressed during the study and were acceptable: recovery, dilution integrity (factor 2 and 5), selectivity (haemolysed, lipaemic and 6 lots of K2 EDTA plasma). No matrix and carryover effects were observed. The presence of the most concomitantly used drugs and compounds did not affected pomalidomide nominal concentrations.

Stability analyses have been performed and approved for following conditions: in biological matrix at -25 ± 10°C for a minimum of 12 hours; four freeze-thaw cycles from -25 ± 10°C to RT; bench top stability at biological matrix for at least 3.00 hours at RT; at least 20.00 hours in the refrigerator at 5 ± 3°C; stability in whole blood for at least 2.00 hours at RT and in an ice-water bath; in the autosampler at approximately 5°C for at least 102.25 hours; stability of processed samples; long term stability of 124 days at -25 ± 10°C and at 5 ± 3°C.

According to the above validation procedure, a bioanalytical assessment was performed – study for the determination of pomalidomide in human plasma using liquid chromatographic tandem mass spectrometric method - Bioanalytical report BSAP-2023-5400 supporting pivotal study 22-741.

A total of 972 human plasma samples were analysed for pomalidomide concentrations using liquid chromatographic tandem mass spectrometric method. Samples were received between December 12th and 13th, 2022, stored at -20°C, and analysed between December 14th and 23rd, 2022. The samples storage conditions – time and temperature cover validated conditions. The calibrators and the QCs were acceptable during the sample analysis (accuracy and precision) for batches tested. The Time 0 levels were below the LLOQ for all patients. The LLOQ was well established, with values not exceeding 5% of Cmax for all patients. According to the applicant, the total number of QC samples included in an analytical batch was at least 5% of the total number of assessed samples.

Incurred sample reproducibility was assessed for 123 samples (12.7%), and the results were acceptable, as the relative differences in repeated samples did not exceed 20% compared to the initial evaluation for 100% of reanalysed samples. The bioanalysis is considered acceptable.

- **Pharmacokinetic variables**

Primary PK parameters were AUCt and Cmax. The plasma pomalidomide PK parameters Cmax, AUCt, AUCinf, Tmax, Kel, and Thalf were estimated using a non-compartmental approach.

- **Statistical methods**

Analysis of variance (ANOVA) (was performed on log-transformed plasma pomalidomide AUCt, AUCinf, and Cmax. Based on log-transformed data, ratios of the geometric means for treatments and the corresponding 90% confidence intervals (CIs) were calculated for AUCt, AUCinf, and Cmax.

Determination of sample size

Sponsor in-house data indicate a CV for pomalidomide Cmax of approximately 19 %. Assuming a 20% intra-subject variability and a difference between the treatment means of 5 % or less, the necessary sample size for an 90% probability of the 90% CI of the treatment means ratio to be within the 80.00 to 125.00% range was estimated to be 25 subjects.

Three (3) extra subjects were included into the study to account for potential dropouts. Therefore, 28 subjects were enrolled into this study. The study was conducted in one group.

- ***Results***

Table 2. Summary of pharmacokinetic parameters for pomalidomide

Parameter	*Trt*	*n*	*Arithmetic Mean (CV%)*	*Geometric Mean*	*Contrast*	*Ratio (%)*	*90% Confidence Interval*	*Intra-Sbj CV(%)*
AUC_t	**A**	27	633.382 (19)	619.206	**A vs B**	102.09	98.82 - 105.47	7
*(hr*ng/mL)*	**B**	27	619.975 (19)	606.538				
AUC_{inf}	**A**	27	644.184 (19)	629.823	**A vs B**	102.12	98.95 - 105.40	7
*(hr*ng/mL)*	**B**	27	630.512 (20)	616.724				
C_{max}	**A**	27	69.633 (24)	67.680	**A vs B**	105.74	99.98 - 111.84	12
(ng/mL)	**B**	27	65.604 (22)	64.005				

CV, coefficient of variation; n, number of subjects in statistical dataset; Sbj, subject; Trt, treatment.

Treatment A (Test Product)	Pomalidomide 4 mg capsules, hard, Batch No.: RA0440
Treatment B (Reference Product)	Imnovid® 4 mg hard capsules (pomalidomide), Batch No.: C2437AH

Figure 2. Mean plasma pomalidomide concentration-time profile linear scale (A: n = 27 / B: n = 27)

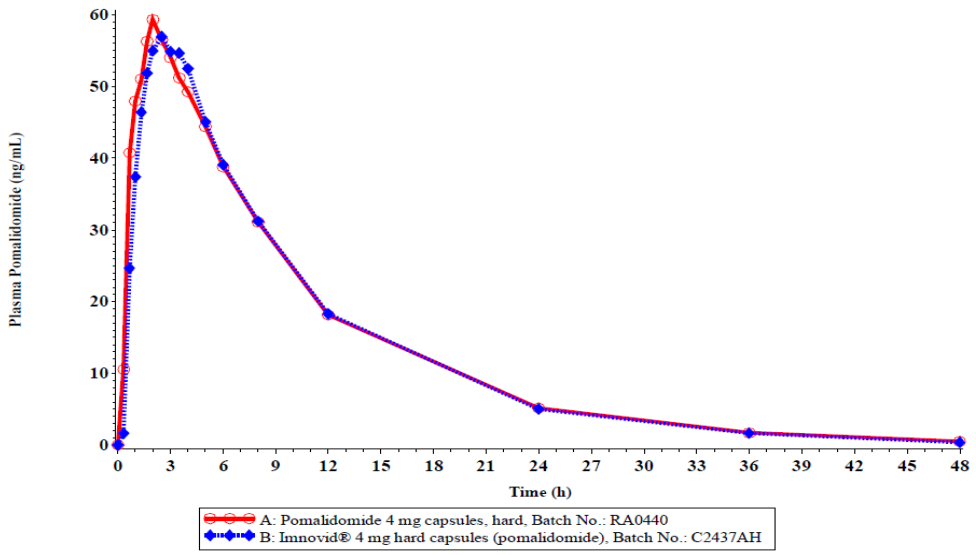


Figure 3. Mean plasma pomalidomide concentration-time profile semi-log scale (A: n = 27 / B: n = 27)

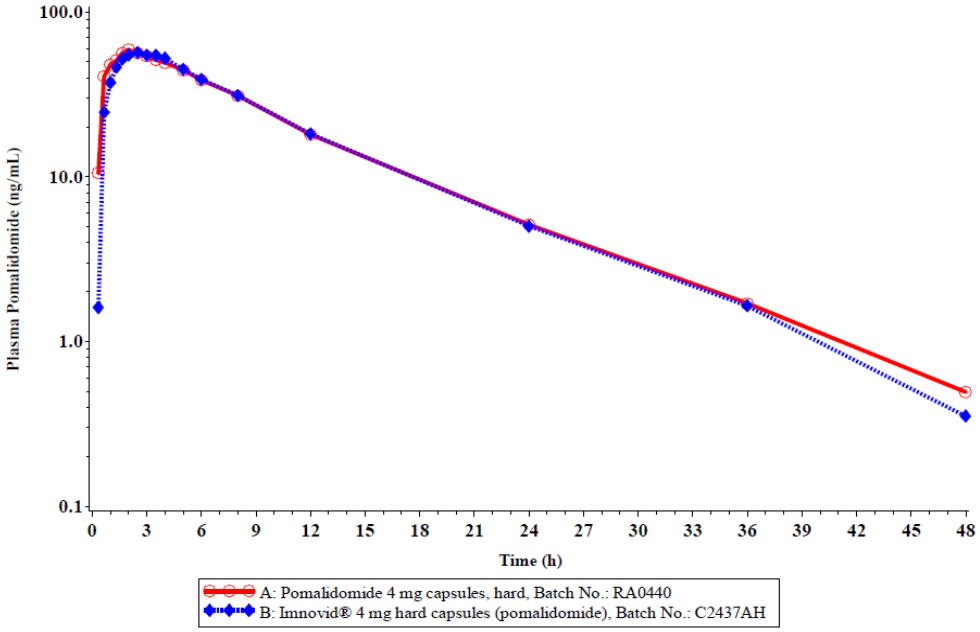


Figure 4. Descriptive statistics for plasma pomalidomide pharmacokinetic parameters

Parameter	*Trt*	*GeoMean*	*ArithMean*	*SD*	*CV%*	*Median*	*Minimum*	*Maximum*	*N*
AUC_t	A	621.053	633.382	123.256	19.46	625.164	371.060	907.636	27
*(hr*ng/mL)*	B	607.953	619.975	120.582	19.45	631.617	386.607	861.006	27
AUC_{inf}	A	631.673	644.184	125.412	19.47	630.478	382.942	917.107	27
*(hr*ng/mL)*	B	618.144	630.512	123.838	19.64	640.017	398.464	896.404	27
AUC_t/AUC_{inf}	A	98.32	98.32	0.82	0.84	98.48	95.18	99.17	27
(%)	B	98.35	98.35	0.76	0.77	98.62	96.05	99.29	27
C_{max}	A	67.781	69.633	16.628	23.88	68.900	40.700	105.000	27
(ng/mL)	B	64.137	65.604	14.622	22.29	62.900	46.800	103.000	27
T_{max}	A	1.65	1.94	1.17	60.02	1.67	0.67	5.00	27
(hr)	B	2.22	2.43	1.08	44.34	2.00	1.00	5.00	27
T_{half}	A	6.92	7.08	1.60	22.66	6.74	4.63	11.85	27
(hr)	B	6.46	6.57	1.25	19.10	6.49	4.64	10.27	27
K_{el}	A	0.1002	0.1023	0.0210	20.55	0.1028	0.0585	0.1498	27
(1/hr)	B	0.1073	0.1089	0.0189	17.39	0.1068	0.0675	0.1493	27
TLIN	A	10.72	13.36	7.78	58.24	12.00	1.33	24.03	27
(hr)	B	8.60	10.47	6.11	58.43	12.00	2.00	24.00	27
R^2	A	0.9979	0.9979	0.0028	0.28	0.9992	0.9894	1.0000	27
	B	0.9986	0.9986	0.0022	0.22	0.9996	0.9901	1.0000	27
Ct	A	0.975	1.037	0.389	37.50	0.955	0.540	2.190	27
(ng/mL)	B	0.996	1.082	0.470	43.40	0.983	0.542	2.390	27
LQCT	A	41.01	41.67	7.23	17.35	47.00	24.00	49.23	27
(hr)	B	39.08	39.67	6.89	17.37	35.75	24.00	48.85	27

TLIN = start time for linear regression
R^2 = coefficient of determination for regression analysis
Ct = last measurable concentration value at LQCT. This value was used for the extrapolation to infinity.
LQCT = time of the last quantifiable concentration
Treatment A: Pomalidomide 4 mg capsules, hard, Batch No.: RA0440
Treatment B: Imnovid® 4 mg hard capsules (pomalidomide), Batch No.: C2437AH

The point estimates and 90% confidence intervals for the ln-transformed pharmacokinetic variables C_{max} and AUC were within the predefined bioequivalence range of 80.00% - 125.00%.

- ***Safety data***

The safety dataset included subjects who received at least one administration of any study treatment. Data from subjects in this dataset were used for the assessment of safety. Accordingly, 28 subjects were included in the safety dataset.

A total of nine treatment-emergent adverse events (TEAEs) were reported by five subjects (17.9% of subjects dosed) during this study. Three TEAEs (constipation, fatigue, and nausea) were assessed as being drug-related (possible relationship to IMP). These, TEAEs affected the same subject, and were reported following Treatment B (Reference Product) administration.

All TEAEs were mild in severity and resolved prior to the end of the study. No serious adverse events were reported during the conduct of this study. Table 3 summarises the frequency of TEAEs that occurred during the conduct of this study.

Table 3. Summary Count of Treatment-Emergent Adverse Events

	Severity			Relationship to the Drug Treatment				Concomitant Medication	
Treatment	Mild	Moderate	Severe	Probable	Possible	Unlikely	Unrelated	DT	NDT
A	3	0	0	0	0	3	0	0	0
B	6	0	0	0	3	2	1	1	0
Total	9	0	0	0	3	5	1	1	0

DT, drug therapy; NDT, non-drug therapy.
Treatment A (Test Product): Pomalidomide 4 mg capsules, hard, Batch No.: RA0440
Treatment B (Reference Product): Imnovid® 4 mg hard capsules (pomalidomide), Batch No.: C2437AH

Analysis of Adverse Events

Five subjects (17.9% of subjects dosed) experienced a total of 9 TEAEs. Three subjects (10.7%) experienced three TEAEs following Treatment A (Test Product) administration, and 3 subjects (10.7%) experienced 6 TEAEs following Treatment B (Reference Product) administration. Three AEs (constipation, fatigue, and nausea) were assessed as being drug related, each AE affecting the same subject.

Vomiting and Diarrhoea

There were no episodes of vomiting during this study. There were no episodes of diarrhoea (defined in the protocol as three episodes of loose stools or one episode of severe loose stools; loose stools being defined as defecation of soft stools that cannot be controlled and severe loose stools being defined as defecation of watery stools that cannot be controlled).

Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

No deaths, SAEs, or other significant AEs occurred during the study.

Vital Signs, Physical Findings and Other Observations Related to Safety

No clinically significant findings were detected from physical examination during this study.

TEAEs observed during this study were represented among the SOCs Eye disorders, affecting one subject (3.6%); gastrointestinal disorders, affecting one subject (3.6%); general disorders and administration site conditions, affecting one subject (3.6%); Musculoskeletal and connective tissue disorders, affecting one subject (3.6%); vascular disorder affecting one subject (3.6%) and nervous system disorders, affecting two subjects (7.1%).

Study 22-725: Comparative, randomised, single-dose, crossover bioavailability study of Pomalidomide 4mg formulation in healthy volunteers under fasting conditions.

Methods

Study Design: Open-label, single-dose, randomised, four treatment, four-period, cross-over study under fasting conditions, with at least 7 days wash-out period between two consecutive study treatment administrations.

In each study period subjects received one single dose of test study medications or reference formulation with 240 mL of room temperature water after at least 10-hour fasting period in compliance with the randomisation scheme.

Duration of Treatment*:* Four periods with a 7 day wash-out period between two consecutive treatments.

The objective of this study was to compare the rate and extent of absorption of pomalidomide from Pomalidomide 4 mg capsules, hard as Treatment A, B and C versus Imnovid 4 mg hard capsules as Treatment D, administered to healthy volunteers in a single-dose, randomised, 4 way cross-over study under fasting conditions.

- **Test and reference products**

Treatment A

Name: Pomalidomide 4 mg capsules, hard
Manufacturer: KRKA-FARMA d.o.o., Jastrebarsko, Republic of Croatia, EU
Dosage form: capsules, hard
Route of administration: oral
Active ingredient: pomalidomide
Strength: 4 mg
Batch No.: Y00742
Manuf. date: 9 February 2022
Re-test date 9 June 2022

Treatment B

Name: Pomalidomide 4 mg capsules, hard
Manufacturer: KRKA-FARMA d.o.o., Jastrebarsko, Republic of Croatia, EU
Dosage form: capsules, hard
Route of administration: oral
Active ingredient: pomalidomide
Strength: 4 mg

Batch No.: Y00743
Manuf. date: 10 February 2022
Re-test date 10 June 2022

Treatment C

Name: Pomalidomide 4 mg capsules, hard
Manufacturer: KRKA-FARMA d.o.o., Jastrebarsko, Republic of Croatia, EU
Dosage form: capsules, hard
Route of administration: oral
Active ingredient: pomalidomide
Strength: 4 mg
Batch No.: Y00744
Manuf. date: 10 February 2022
Re-test date 10 June 2022

Treatment D

Name: Imnovid 4 mg hard capsules
Manufacturer: Celgene Distribution B.V., The Netherlands, EU
MAH: Celgene Europe B.V., The Netherlands, EU
Dosage form: hard capsules
Route of administration: oral
Active ingredient: pomalidomide
Strength: 4 mg
Batch No.: C2329A
Expiry date: January 2024
Country/Market of Origin: Denmark, EU

Both the reference and the test products are identical with regards to the strength and formulation intended to be marketed.

- **Population studied**

Healthy adult male volunteers aged between ≥18 to ≤65 years, with BMI within 18.5-30 kg/m2, Caucasian race, non-smokers or ex-smokers (an ex-smoker being defined as someone who did not use nicotine/ tobacco-containing products in the last 6 months prior to screening).

Subjects were in good health as determined by the medical exam and medication history, complete physical examination (including vital signs), ECG and clinical laboratory tests (haematology, biochemical profile, urinalysis), including negative HIV, Hepatitis B and Hepatitis C tests performed at screening, Complete blood count (CBC) test, COVID-19 PCR test as well as a negative urine screen for drugs of abuse, alcohol test and cotinine test at check-in before each study period.

Planned to be dosed: 18
Dosed in Period 1: 18
Dosed in Period 2: 18
Dosed in Period 3: 16
Dosed in Period 4: 16

Sixteen healthy subjects completed all study periods. Two subjects (one each from the reference and the 4mg of the test product) did not complete the study for personal reasons. The pharmacokinetic/statistical evaluation included all 18 subjects.

Protocol deviations

No major protocol deviations were reported.

- **Analytical methods**

The aim of the analysis submitted in report PMD-V5-654(R2) was to validate an HPLC method using MS/MS detection for determination of pomalidomide in human plasma to support pilot study 22-725. The analysis of pomalidomide was validated in the linear ranges of the analyte from 0.500 ng/mL to 150.000 ng/mL. QC sample for pomalidomide were 0.500 ng/mL, 1.500 ng/mL, 10.000 ng/mL, 75.000 ng/mL and 112.500 ng/mL.

Between-run accuracy was between 96.4%-110%, between run-precision ranged from 3.8 to 6.3%, within run accuracy from 98.0 to 113.1%, and within run precision from 1.0 to 6.0%.

Following other parameters were addressed during the study and were acceptable: selectivity (in the presence of the major metabolites, and after potential conversion during storage), specificity (in the presence of 10 different matrices and the most concomitantly used drugs and compounds), sensitivity (0.500 ng/mL), dilution integrity (2x). No matrix and carryover effects were observed.

Stability analyses has been for following conditions: short term in whole blood ice/water bath for 2.4 hours, short-term in huma plasma at 4°C for 26.4 hours and without preservative for 2.0 hours; short-term solution stability in ACN:H2O 50:50% v/v at 22°C for 22.6 hours, long-term solution stability in ACN:H2O 50:50% v/v at 4°C for 11 and 45 days, long-term solution stability of pomalidomide-15N-13C5 in ACN:H2O 50:50% v/v at 4°C for 11, 45 and 352 days, long-term stability in human plasma at -80°C for 7 days and 41 days.

According to the above validation procedure, a bioanalytical assessment was performed – study for the determination of pomalidomide in human plasma using HPLC with MS/MS detection - Bioanalytical report N° KRS-P4-482 supporting pilot study 22-725.

A total of 1156 human plasma samples were analysed for pomalidomide concentrations using HPLC with MS/MS detection. The samples were stored for a maximum of 40 days, a storage condition that falls within validated conditions (maximum validated at -80°C for 41 days). The calibrators and the QCs were acceptable during the sample analysis (accuracy and precision) for runs tested. The Time 0 levels were below the LLOQ for all patients across the four tested periods. The LLOQ was well established, with values not exceeding 5% of Cmax for all patients and periods. Three samples were repeated due to the analytical reasons (no or unexpected internal standard results). No samples were manually reintegrated for Pomalidomide and Pomalidomide-15N-13C5 in acceptable or rejected subject sample runs.

- **Pharmacokinetic variables**

AUCt, AUCi, Cmax, residual area (RAUC), Tmax, Thalf and Kel. The selected pharmacokinetic variables and methods are adequate.

- **Statistical methods**

Analysis of variance (ANOVA) was performed on the ln-transformed AUCi, AUCt and Cmax parameters for pomalidomide. Consistent with the two one-sided tests for bioequivalence, 90% confidence intervals was calculated for the Test to Reference ratios of least-squares means for parameters AUCi, AUCt and Cmax using ln-transformed data. Descriptive statistics were also done for all pharmacokinetic parameters.

Statistical methods are acceptable.

- ***Results***

Table 4. 90% confidence intervals of ratio of LS-means (Test/Ref); Analyte: pomalidomide: (N=18)

Test	Dependent	FormRef	Ratio_%Ref_	CI_90_Lower	CI_90_Upper
A	Ln(AUCt)	D	99.93	94.62	105.54
	Ln(AUCi)	D	99.84	94.66	105.30
	Ln(Cmax)	D	108.20	97.08	120.59
B	Ln(AUCt)	D	103.42	97.78	109.40
	Ln(AUCi)	D	103.70	98.17	109.54
	Ln(Cmax)	D	102.95	92.09	115.09
C	Ln(AUCt)	D	102.47	97.01	108.23
	Ln(AUCi)	D	102.72	97.38	108.35
	Ln(Cmax)	D	74.41	66.75	82.95

Figure 5. Mean concentrations: study code: 22-725; Analyte: pomalidomide in plasma/blood concentration-time profiles linear plot

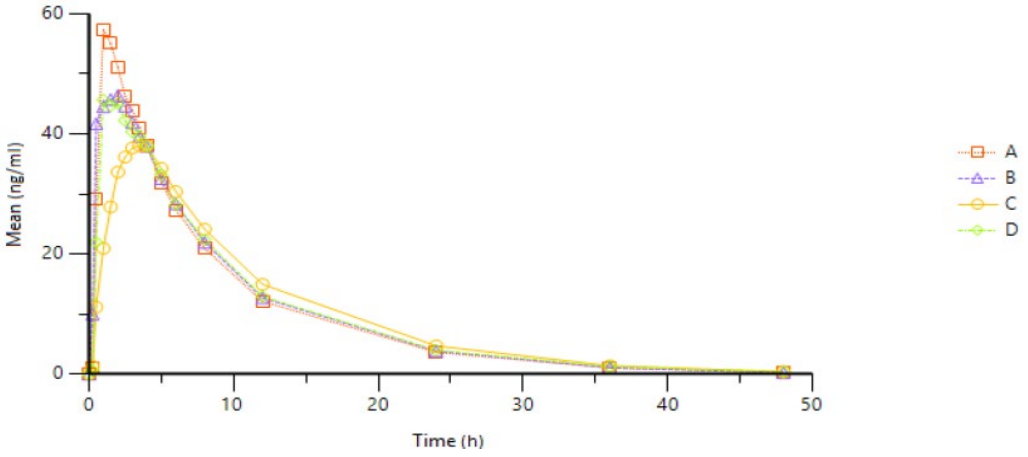
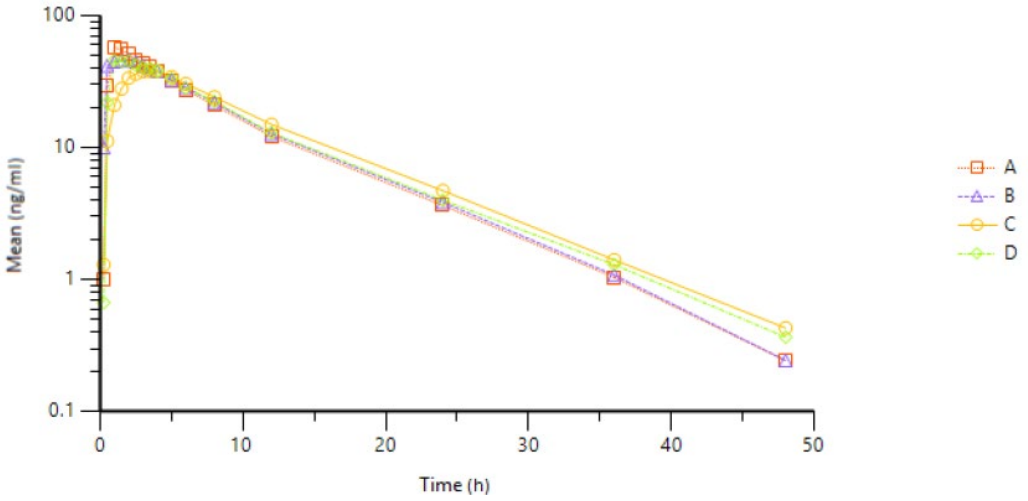


Figure 6. Mean concentrations: Study code: 22-725; Analyte: pomalidomide in plasma/blood concentration-time profiles log-linear plot



The 90% confidence intervals of the ratios of LS-Means derived from analyses on the lntransformed PK parameters AUCt, AUCi and Cmax for pomalidomide were within the 80.00- 125.00% acceptance range under fasting condition for test treatments A and B.

- ***Safety data***

All treatments (A, B, C and D) appear to be safe and well tolerated after a single oral dose of pomalidomide 4 mg under fasting condition in healthy male volunteers.

A total of 1 post-dose adverse event was reported by 1 (5.56%) of the 18 subjects who received at least one dose of the study medication. The AE occurred after administration of Treatment A.

No safety concerns are expected since AE was mild in severity and resolved/recovered by the end of the study. The relationship of AE with the Study medication was judged as probable.

No severe adverse events, serious adverse events or deaths occurred during the study.

Upon conclusion of the clinical portion of the study, the results from the subjects who completed end of study procedures, including laboratory tests and vital signs measurement confirmed the absence of significant changes in the subject's state of health.

No new safety concerns related to administered formulations were raised during the conduct of this study.

2.4.2.2. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.3. Discussion on clinical aspects

This application concerns a generic version of pomalidomide, capsules, hard. The reference product Imnovid 1 mg, 2 mg, 3 mg, 4 mg capsule, hard is indicated in combination with bortezomib and dexamethasone in the treatment of adult patients with multiple myeloma who have received at least

one prior treatment regimen including lenalidomide and in combination with dexamethasone in the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy.

From a clinical perspective, this application does not contain any new data on pharmacodynamics, efficacy and safety of the active substance. However, the summary of the available data provided by the applicant is considered sufficient.

The applicant conducted two studies to support this MAA.

Pivotal Study 22-741 was an open-label, single-dose, randomised, two-period, two-treatment, two-sequence, crossover, bioequivalence study, designed to evaluate the bioequivalence of pomalidomide 4mg between a test product Pomalidomide 4mg hard capsules and a reference product Imnovid 4 mg hard capsules in 27 healthy volunteers under fasting conditions. The overall design of the study is considered acceptable. Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated.

Pharmacokinetic and statistical methods applied in this study were adequate.

The plasma pomalidomide PK parameters Cmax, AUCt, AUCinf, Tmax, Kel, and Thalf were estimated using a non-compartmental approach. Study subjects were administered the dose of the highest applied strength of 4 mg, which is in line with CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **. The washout period of 7 days is appropriate. The chosen time points for blood samples collection are acceptable. The choice of the EU reference product, sourced from Denmark is appropriate.

The test formulation of Pomalidomide 4 mg hard capsules met the protocol-defined criteria for bioequivalence when compared with the reference product Imnovid 4mg. The point estimates and their 90% confidence intervals for the parameters AUC0-t, AUC0-∞, and Cmax were all contained within the protocol-defined acceptance range of 80.00% to 125.00%. Bioequivalence of the two formulations was demonstrated.

No serious adverse events were reported during the conduct of this study. A total of 9 mild TEAEs were reported in 5 subjects during the study. Three TEAEs (constipation, fatigue, and nausea) were considered treatment-related. There were no significant differences in safety concerns after administration of the Test and the Reference products.

The applicant also submitted the results from a pilot open-label, single-dose, randomised, four treatment, four-period, cross-over Study 22-725 under fasting conditions, with at least 7 days wash-out period between two consecutive study treatment administrations to compare the rate and extent of absorption of pomalidomide from Pomalidomide 4 mg capsules, hard as Treatment A, B and C versus Imnovid 4 mg hard capsules as Treatment D. The overall design of the study is considered acceptable. Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated.

Pharmacokinetic and statistical methods applied in this study were adequate.

The 90% confidence intervals of the ratios of LS-means derived from analyses on the lntransformed PK parameters AUCt, AUCi and Cmax for pomalidomide were within the 80.00- 125.00% acceptance range under fasting condition for test treatments A and B.

Based on these results, Pomalidomide 4 mg capsules, hard and Reference Imnovid 4 mg hard capsules are bioequivalent after single-dose administration under fasting condition.

No new concerning safety finding were reported in the study.

The requested biowaiver for the additional strengths 1mg, 2 mg and 3 mg strengths is acceptable.

2.4.4. Conclusions on clinical aspects

Based on the presented bioequivalence study (22-741) Pomalidomide Krka 4 mg hard capsules is considered bioequivalent with Imnovid 4mg hard capsules.

The results of study 22-741 with the 4mg formulation can be extrapolated to other strengths 1mg, 2mg, 3mg, according to conditions in the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1, section 4.1.6.

2.5. Risk Management Plan

2.5.1. Safety concerns

Table 5. Summary of safety concerns

Important identified risks	Teratogenicity
	Severe infection due to neutropenia and pancytopenia
	Thrombocytopenia and bleeding
	Cardiac failure
	Non-melanoma skin cancer
Important potential risks	Other second primary malignancies
	Cardiac arrhythmia
Missing information	None

2.5.2. Pharmacovigilance plan

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
Monitoring of Pregnancy prevention programme implementation (category 3 study) Status: Planned	Monitoring of implementation of PPP	*Teratogenicity*	Routine PSURs in line with DLP of the latest EURD list	Data will be reviewed on an on-going basis as a part of signal detection and reported within PSURs with in-line with EURD list

2.5.3. Risk minimisation measures

Safety concern	Risk minimisation measures
Teratogenicity	**Routine risk minimisation measures:** SmPC Section 4.3., Section 4.4., Section 4.6, Section 4.8, Section 5.3 PL Section 2 and 4. Legal status: Pomalidomide is subject to restricted medical prescription. **Additional risk minimisation measures:** Pomalidomide Pregnancy Prevention Programme (PPP) - Educational programme for healthcare professionals and patients: o Educational HCP kit (Educational healthcare professional brochure, Educational brochures for patients, Patient card, Risk awareness forms, and information on where to find latest SmPC.), - Therapy management • Criteria for determining WCBP, Contraceptive measures and pregnancy testing for WCBP • Advice in SmPC and educational materials - System to ensure appropriate measures have been completed • Patient card or equivalent tool to document childbearing status, counselling and pregnancy testing.
Severe infection due to neutropenia and pancytopenia	**Routine risk minimisation measures:** SmPC Section 4.2., Section 4.4., Section 4.8. PL Section 2 and 4 Legal status: Pomalidomide is subject to restricted medical prescription. **Additional risk minimisation measures:** No risk minimisation measures.
Thrombocytopenia and bleeding	**Routine risk minimisation measures:** SmPC Section 4.2., Section 4.4., Section 4.8. PL Section 2 and 4

Safety concern	Risk minimisation measures
	Legal status: Pomalidomide is subject to restricted medical prescription. **Additional risk minimisation measures:** - Educational HCP brochure - Educational brochure for patients
Cardiac failure	**Routine risk minimisation measures:** SmPC Section 4.4., Section 4.8. PL Section 2 and 4 Legal status: Pomalidomide is subject to restricted medical prescription. **Additional risk minimisation measures:** Educational HCP brochure
Non-melanoma skin cancer	**Routine risk minimisation measures:** SmPC Section 4.4., Section 4.8. PL Section 2 and 4. Legal status: Pomalidomide is subject to restricted medical prescription. **Additional risk minimisation measures:** No risk minimisation measures
Other second primary malignancies	**Routine risk minimisation measures:** SmPC Section 4.4. PL Section 2 Legal status: Pomalidomide is subject to restricted medical prescription. **Additional risk minimisation measures:** No risk minimisation measures
Cardiac arrhythmia	**Routine risk minimisation measures:** SmPC Section 4.8.

Safety concern	Risk minimisation measures
	PL Section 4 Legal status: Pomalidomide is subject to restricted medical prescription. **Additional risk minimisation measures:** No risk minimisation measures

2.5.4. Conclusion

The CHMP and PRAC considered that the risk management plan version 0.4 is acceptable.

2.6. Pharmacovigilance

2.6.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.6.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.7. Product information

2.7.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Bortezomib Krka 3,5 mg powder for solution for injection and to Imnovid 1 mg, 2mg, 3mg, 4mg hard capsules. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-risk balance

This application concerns a generic version of pomalidomide, capsules, hard. The reference product Imnovid 1 mg, 2 mg, 3 mg, 4 mg capsule, hard is indicated in combination with bortezomib and dexamethasone is indicated in the treatment of adult patients with multiple myeloma who have received at least one prior treatment regimen including lenalidomide and in combination with dexamethasone is indicated in the treatment of adult patients with relapsed and refractory multiple

myeloma who have received at least two prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy. No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

The bioequivalence study 22-741 forms the pivotal basis with an open-label, single-dose, randomised, two-period, two-treatment, two-sequence, crossover design in healthy volunteers under fasting conditions to evaluate the bioequivalence of pomalidomide 4mg between a test product Pomalidomide 4mg hard capsules and a reference product Imnovid 4 mg hard capsules.

The study design is considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied are adequate.

The test formulation of Pomalidomide 4mg hard capsules met the protocol-defined criteria for bioequivalence when compared with the Imnovid 4 mg hard capsules. The point estimates and their 90% confidence intervals for the parameters AUC0-t, AUC0-∞, and Cmax were all contained within the protocol-defined acceptance range of 80.00 to 125.00%. Bioequivalence of the two formulations was demonstrated.

A benefit/risk ratio comparable to the reference product can be concluded.

Having considered the data submitted in the application and available on the chosen reference medicinal product, no additional risk minimisation activities are required beyond those included in the product information.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Pomalidomide Krka is not similar to Abecma (Idecabtagene vicleucel), Blenrep (Belantamab mafodotin), Carvykti (Ciltacabtagene autoleucel), Darzalex (Daratumumab), Farydak (Panobinostat), Kyprolis (Carfilzomib), Ninlaro (Ixazomib), and Talvey (talquetamab) within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Pomalidomide Krka is favourable in the following indications:

Pomalidomide Krka in combination with bortezomib and dexamethasone is indicated in the treatment of adult patients with multiple myeloma who have received at least one prior treatment regimen including lenalidomide.

Pomalidomide Krka in combination with dexamethasone is indicated in the treatment of adult patients with relapsed and refractory multiple myeloma who have received at least two prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- ***Periodic Safety Update Reports***

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

1. The MAH shall agree the details of a controlled access programme with the National Competent Authorities and must implement such programme nationally to ensure that:
    - prior to prescribing (where appropriate, and in agreement with the National Competent Authority, dispensing) all healthcare professionals who intend to prescribe (and dispense) Pomalidomide Krka are provided with an Educational Healthcare Professional's Kit containing the following:
        - Educational Healthcare Professional brochure
        - Educational brochures for patients
        - Patient card Risk awareness forms
        - Information on where to find latest Summary of Product Characteristics (SmPC)
2. The MAH shall implement a pregnancy prevention programme (PPP) in each Member State. Details of the PPP should be agreed with the National Competent Authorities in each Member State and put in place prior to the launch of the medicinal product.
3. The MAH should agree the contents of the Educational Healthcare Professional's Kit with the National Competent Authority in each Member State prior to launch of the medicinal product and ensure that the materials contain the key elements as described below.
4. The MAH should agree on the implementation of the controlled access programme in each Member State.

Key elements to be included

Educational Healthcare Professional's Kit
The Educational Healthcare Professional's Kit shall contain the following elements:

Educational Healthcare Professional brochure

- Brief background on pomalidomide
- Maximum duration of treatment prescribed
    - 4 weeks for women with childbearing potential
    - 12 weeks for men and women without childbearing potential

- The need to avoid foetal exposure due to teratogenicity of pomalidomide in animals and the expected teratogenic effect of pomalidomide in humans
- Guidance on handling the blister or capsule of Pomalidomide Krka for healthcare professionals and caregivers
- Obligations of the healthcare professionals who intend to prescribe or dispense Pomalidomide Krka
    - Need to provide comprehensive advice and counselling to patients
    - That patients should be capable of complying with the requirements for the safe use of Pomalidomide Krka
    - Need to provide patients with appropriate patient educational brochure, patient card and/or equivalent tool
- Safety advice relevant to all patients
    - Description and management of thrombocytopenia including incidence rates from clinical studies
    - Description and management of cardiac failure
    - Local country specific arrangements for a prescription for pomalidomide to be dispensed
    - That any unused capsules should be returned to the pharmacist at the end of the treatment
    - That the patient should not donate blood during treatment (including during dose interruptions) and for at least 7 days following discontinuation of Pomalidomide Krka

- Description of the PPP and categorisation of patients based on sex and childbearing potential
    - Algorithm for implementation of PPP
    - Definition of women of childbearing potential (WCBP) and actions the prescriber should take if unsure

- Safety advice for women of childbearing potential
    - The need to avoid foetal exposure
    - Description of the PPP
    - Need for effective contraception (even if the woman has amenorrhoea) and definition of effective contraception
    - That if she needs to change or stop using her method of contraception she should inform:
        - The physician prescribing her contraception that she is on pomalidomide
        - The physician prescribing pomalidomide that she has stopped or changed her method of contraception
    - Pregnancy test regime
        - Advice on suitable tests

        - Before commencing treatment
        - During treatment based on method of contraception
        - After finishing treatment
    - Need to stop Pomalidomide Krka immediately upon suspicion of pregnancy
    - Need to tell treating doctor immediately upon suspicion of pregnancy

- Safety advice for men
    - The need to avoid foetal exposure
    - The need to use condoms if sexual partner is pregnant or a WCBP not using effective contraception (even if the man has had a vasectomy)
        - During Pomalidomide Krka treatment
        - For at least 7 days following final dose
    - That he should not donate semen or sperm during treatment (including during dose interruptions) and for at least 7 days following discontinuation of Pomalidomide Krka treatment
    - That if his partner becomes pregnant whilst he is taking Pomalidomide Krka or shortly after he has stopped taking Pomalidomide Krka he should inform his treating doctor immediately

- Requirements in the event of pregnancy
    - Instructions to stop Pomalidomide Krka immediately upon suspicion of pregnancy, if female patient
    - Need to refer patient to physician specialised or experienced in dealing with teratology and its diagnosis for evaluation and advice
    - Local contact details for reporting of any suspected pregnancy immediately
    - Pregnancy reporting form

- Local contact details for reporting adverse reactions

Educational Brochures for patients

The Educational brochures for patients should be of 3 types:

- Brochure for women patients of childbearing potential and their partner
- Brochure for women patients who are not of childbearing potential
- Brochure for male patients

All educational brochures for patients should contain the following elements:

- That pomalidomide is teratogenic in animals and is expected to be teratogenic in humans
- That pomalidomide may cause thrombocytopenia and the need for regular blood tests
- Description of the patient card and its necessity
- Guidance on handling Pomalidomide Krka for patients, caregivers and family members
- National or other applicable specific arrangements for a prescription for Pomalidomide Krka to be dispensed
- That the patient must not give Pomalidomide Krka to any other person
- That the patient should not donate blood during treatment (including during dose interruptions) and for at least 7 days after discontinuation of Pomalidomide Krka treatment

- That the patient should tell their doctor about any adverse events

- That any unused capsules should be returned to the pharmacist at the end of the treatment

The following information should also be provided in the appropriate brochure:

Brochure for women patients with childbearing potential

- The need to avoid foetal exposure
- Description of the PPP
- The need for effective contraception and definition of effective contraception
- That if she needs to change or stop using her method of contraception she should inform:
    - The physician prescribing her contraception that she is on pomalidomide
    - The physician prescribing pomalidomide that she has stopped or changed her method of contraception

- Pregnancy test regime
    - Before commencing treatment
    - During treatment (including dose interruptions), at least every 4 weeks except in case of confirmed tubal sterilisation
    - After finishing treatment
- The need to stop Pomalidomide Krka immediately upon suspicion of pregnancy
- The need to contact their doctor immediately upon suspicion of pregnancy

Brochure for male patients

- The need to avoid foetal exposure
- The need to use condoms if sexual partner is pregnant or a WCBP and not using effective contraception (even if the man has had vasectomy)
    - During Pomalidomide Krka treatment (including dose interruptions)
    - For at least 7 days following final dose
- That if his partner becomes pregnant, he should inform his treating doctor immediately
- That he should not donate semen or sperm during treatment (including during dose interruptions) and for at least 7 days following discontinuation of Pomalidomide Krka treatment

Patient Card or equivalent tool

The patient card shall contain the following elements:

- Verification that appropriate counselling has taken place
- Documentation of childbearing potential status
- Check box (or similar) which physician ticks to confirm that patient is using effective contraception (if woman of childbearing potential)
- Pregnancy test dates and results

Risk Awareness Forms

There should be 3 types of risk awareness forms:

- Women of childbearing potential
- Women of non-childbearing potential
- Male patient

All risk awareness forms should contain the following elements:

- teratogenicity warning
- patients receive the appropriate counselling prior to treatment initiation
- affirmation of patient understanding regarding the risk of pomalidomide and the PPP measures

- date of counselling
- patient details, signature and date
- prescriber name, signature and date
- aim of this document i.e. as stated in the PPP: "The aim of the risk awareness form is to protect patients and any possible foetuses by ensuring that patients are fully informed of and understand the risk of teratogenicity and other adverse reactions associated with the use of pomalidomide. It is not a contract and does not absolve anybody from his/her responsibilities with regard to the safe use of the product and prevention of foetal exposure."

Risk awareness forms for women of childbearing potential should also include:
- Confirmation that the physician has discussed the following:

    - the need to avoid foetal exposure
    - that if she is pregnant or plans to be, she must not take pomalidomide
    - that she understands the need to avoid pomalidomide during pregnancy and to apply effective contraceptive measures without interruption, at least 4 weeks before starting treatment, throughout the entire duration of treatment, and at least 4 weeks after the end of treatment
    - that if she needs to change or stop using her method of contraception she should inform:
        - the physician prescribing her contraception that she is taking Pomalidomide Krka
        - the physician prescribing Pomalidomide Krka that she has stopped or changed her method of contraception
    - of the need for pregnancy tests i.e. before treatment, at least every 4 weeks during treatment and after treatment
    - of the need to stop Pomalidomide Krka immediately upon suspicion of pregnancy
    - of the need to contact their doctor immediately upon suspicion of pregnancy
    - that she should not share the medicinal product with any other person
    - that she should not donate blood during treatment (including during dose interruptions) and for at least 7 days following discontinuation of Pomalidomide Krka

    - that she should return the unused capsules to the pharmacist at the end of treatment

Risk awareness forms for women with no childbearing potential should also include:
- Confirmation that the physician has discussed the following:
    - that she should not share the medicinal product with any other person
    - that she should not donate blood during treatment (including during dose interruptions) and for at least 7 days following discontinuation of Pomalidomide Krka
    - that she should return the unused capsules to the pharmacist at the end of treatment

Risk awareness forms for male patients should also include:
- Confirmation that the physician has discussed the following:
    - the need to avoid foetal exposure
    - that pomalidomide is found in semen and the need to use condoms if sexual partner is pregnant or is a WCBP not on effective contraception (even if the man has had a vasectomy)

- that if his partner becomes pregnant, he should inform his treating doctor immediately and always use a condom
- that he should not share the medicinal product with any other person
- that he should not donate blood or semen during treatment (including during dose interruptions) and for at least 7 days following discontinuation of Pomalidomide Krka
- that he should return the unused capsules to the pharmacist at the end of treatment

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

1. The MAH shall agree the details of a controlled access programme with the National Competent Authorities and must implement such programme nationally to ensure that:
   - prior to prescribing (where appropriate, and in agreement with the National Competent Authority, dispensing) all healthcare professionals who intend to prescribe (and dispense) Pomalidomide Krka are provided with an Educational Healthcare Professional's Kit containing the following:
     - Educational Healthcare Professional brochure
     - Educational brochures for patients
     - Patient card Risk awareness forms
     - Information on where to find latest Summary of Product Characteristics (SmPC)
2. The MAH shall implement a pregnancy prevention programme (PPP) in each Member State. Details of the PPP should be agreed with the National Competent Authorities in each Member State and put in place prior to the launch of the medicinal product.
3. The MAH should agree the contents of the Educational Healthcare Professional's Kit with the National Competent Authority in each Member State prior to launch of the medicinal product and ensure that the materials contain the key elements as described below.
4. The MAH should agree on the implementation of the controlled access programme in each Member State.

Key elements to be included

Educational Healthcare Professional's Kit
The Educational Healthcare Professional's Kit shall contain the following elements:

Educational Healthcare Professional brochure

- Brief background on pomalidomide
- Maximum duration of treatment prescribed
  - 4 weeks for women with childbearing potential
  - 12 weeks for men and women without childbearing potential

- The need to avoid foetal exposure due to teratogenicity of pomalidomide in animals and the expected teratogenic effect of pomalidomide in humans
- Guidance on handling the blister or capsule of Pomalidomide Krka for healthcare professionals and caregivers
- Obligations of the healthcare professionals who intend to prescribe or dispense Pomalidomide Krka
  - Need to provide comprehensive advice and counselling to patients
  - That patients should be capable of complying with the requirements for the safe use of Pomalidomide Krka

- Need to provide patients with appropriate patient educational brochure, patient card and/or equivalent tool

- Safety advice relevant to all patients
  - Description and management of thrombocytopenia including incidence rates from clinical studies
  - Description and management of cardiac failure
  - Local country specific arrangements for a prescription for pomalidomide to be dispensed
  - That any unused capsules should be returned to the pharmacist at the end of the treatment
  - That the patient should not donate blood during treatment (including during dose interruptions) and for at least 7 days following discontinuation of Pomalidomide Krka

- Description of the PPP and categorisation of patients based on sex and childbearing potential
  - Algorithm for implementation of PPP
  - Definition of women of childbearing potential (WCBP) and actions the prescriber should take if unsure

- Safety advice for women of childbearing potential
  - The need to avoid foetal exposure
  - Description of the PPP
  - Need for effective contraception (even if the woman has amenorrhoea) and definition of effective contraception
  - That if she needs to change or stop using her method of contraception she should inform:
    - The physician prescribing her contraception that she is on pomalidomide
    - The physician prescribing pomalidomide that she has stopped or changed her method of contraception
  - Pregnancy test regime
    - Advice on suitable tests
    - Before commencing treatment
    - During treatment based on method of contraception
    - After finishing treatment
  - Need to stop Pomalidomide Krka immediately upon suspicion of pregnancy
  - Need to tell treating doctor immediately upon suspicion of pregnancy

- Safety advice for men
  - The need to avoid foetal exposure
  - The need to use condoms if sexual partner is pregnant or a WCBP not using effective contraception (even if the man has had a vasectomy)
    - During Pomalidomide Krka treatment
    - For at least 7 days following final dose
  - That he should not donate semen or sperm during treatment (including during dose interruptions) and for at least 7 days following discontinuation of Pomalidomide Krka treatment
  - That if his partner becomes pregnant whilst he is taking Pomalidomide Krka or shortly after he has stopped taking Pomalidomide Krka he should inform his treating doctor immediately

- Requirements in the event of pregnancy

    - Instructions to stop Pomalidomide Krka immediately upon suspicion of pregnancy, if female patient
    - Need to refer patient to physician specialised or experienced in dealing with teratology and its diagnosis for evaluation and advice
    - Local contact details for reporting of any suspected pregnancy immediately
    - Pregnancy reporting form

- Local contact details for reporting adverse reactions

Educational Brochures for patients

The Educational brochures for patients should be of 3 types:

- Brochure for women patients of childbearing potential and their partner
- Brochure for women patients who are not of childbearing potential
- Brochure for male patients

All educational brochures for patients should contain the following elements:

- That pomalidomide is teratogenic in animals and is expected to be teratogenic in humans
- That pomalidomide may cause thrombocytopenia and the need for regular blood tests
- Description of the patient card and its necessity
- Guidance on handling Pomalidomide Krka for patients, caregivers and family members
- National or other applicable specific arrangements for a prescription for Pomalidomide Krka to be dispensed
- That the patient must not give Pomalidomide Krka to any other person
- That the patient should not donate blood during treatment (including during dose interruptions) and for at least 7 days after discontinuation of Pomalidomide Krka treatment

- That the patient should tell their doctor about any adverse events
- That any unused capsules should be returned to the pharmacist at the end of the treatment

The following information should also be provided in the appropriate brochure:

Brochure for women patients with childbearing potential

- The need to avoid foetal exposure
- Description of the PPP
- The need for effective contraception and definition of effective contraception
- That if she needs to change or stop using her method of contraception she should inform:
    - The physician prescribing her contraception that she is on pomalidomide
    - The physician prescribing pomalidomide that she has stopped or changed her method of contraception

- Pregnancy test regime
    - Before commencing treatment
    - During treatment (including dose interruptions), at least every 4 weeks except in case of confirmed tubal sterilisation
    - After finishing treatment
- The need to stop Pomalidomide Krka immediately upon suspicion of pregnancy
- The need to contact their doctor immediately upon suspicion of pregnancy

Brochure for male patients

- The need to avoid foetal exposure
- The need to use condoms if sexual partner is pregnant or a WCBP and not using effective contraception (even if the man has had vasectomy)
    - During Pomalidomide Krka treatment (including dose interruptions)
    - For at least 7 days following final dose
- That if his partner becomes pregnant, he should inform his treating doctor immediately
- That he should not donate semen or sperm during treatment (including during dose interruptions) and for at least 7 days following discontinuation of Pomalidomide Krka treatment

Patient Card or equivalent tool

The patient card shall contain the following elements:

- Verification that appropriate counselling has taken place
- Documentation of childbearing potential status
- Check box (or similar) which physician ticks to confirm that patient is using effective contraception (if woman of childbearing potential)
- Pregnancy test dates and results

Risk Awareness Forms

There should be 3 types of risk awareness forms:

- Women of childbearing potential
- Women of non-childbearing potential
- Male patient

All risk awareness forms should contain the following elements:

- teratogenicity warning
- patients receive the appropriate counselling prior to treatment initiation
- affirmation of patient understanding regarding the risk of pomalidomide and the PPP measures
- date of counselling
- patient details, signature and date
- prescriber name, signature and date
- aim of this document i.e. as stated in the PPP: "The aim of the risk awareness form is to protect patients and any possible foetuses by ensuring that patients are fully informed of and understand the risk of teratogenicity and other adverse reactions associated with the use of pomalidomide. It is not a contract and does not absolve anybody from his/her responsibilities with regard to the safe use of the product and prevention of foetal exposure."

Risk awareness forms for women of childbearing potential should also include:

- Confirmation that the physician has discussed the following:
    - the need to avoid foetal exposure
    - that if she is pregnant or plans to be, she must not take pomalidomide
    - that she understands the need to avoid pomalidomide during pregnancy and to apply effective contraceptive measures without interruption, at least 4 weeks before starting treatment, throughout the entire duration of treatment, and at least 4 weeks after the end of treatment
    - that if she needs to change or stop using her method of contraception she should inform:

        - the physician prescribing her contraception that she is taking Pomalidomide Krka
        - the physician prescribing Pomalidomide Krka that she has stopped or changed her method of contraception
    - of the need for pregnancy tests i.e. before treatment, at least every 4 weeks during treatment and after treatment
    - of the need to stop Pomalidomide Krka immediately upon suspicion of pregnancy
    - of the need to contact their doctor immediately upon suspicion of pregnancy
    - that she should not share the medicinal product with any other person
    - that she should not donate blood during treatment (including during dose interruptions) and for at least 7 days following discontinuation of Pomalidomide Krka

    - that she should return the unused capsules to the pharmacist at the end of treatment

Risk awareness forms for women with no childbearing potential should also include:
- Confirmation that the physician has discussed the following:
    - that she should not share the medicinal product with any other person
    - that she should not donate blood during treatment (including during dose interruptions) and for at least 7 days following discontinuation of Pomalidomide Krka
    - that she should return the unused capsules to the pharmacist at the end of treatment

Risk awareness forms for male patients should also include:
- Confirmation that the physician has discussed the following:
    - the need to avoid foetal exposure
    - that pomalidomide is found in semen and the need to use condoms if sexual partner is pregnant or is a WCBP not on effective contraception (even if the man has had a vasectomy)
    - that if his partner becomes pregnant, he should inform his treating doctor immediately and always use a condom
    - that he should not share the medicinal product with any other person
    - that he should not donate blood or semen during treatment (including during dose interruptions) and for at least 7 days following discontinuation of Pomalidomide Krka
    - that he should return the unused capsules to the pharmacist at the end of treatment

These conditions fully reflect the advice received from the PRAC.